

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the above-identified application.

Listing of Claims:

1. (Currently amended) An isolated nucleic acid comprising a polynucleotide selected from the group consisting of:

(1) a first polynucleotide that encodes a polypeptide selected from the group consisting of
(i) an SCN5A polypeptide having a histidine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively,

(ii) an SCN5A polypeptide having an arginine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively,

(iii) an SCN5A polypeptide having a histidine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, and

(iv) an SCN5A polypeptide having an arginine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted,

(2) a second polynucleotide that is at least 80% identical to the first polynucleotide over the entire length of the first polypeptide and that encodes an arginine at amino acid position 1027,

(3) a third polynucleotide that encodes any of the SCN5A polypeptides with a conservative substitution, deletion or rearrangement at one or more non-critical amino acid position and that encodes an arginine at amino acid position 1027, and

(4) a fourth polynucleotide that is a complement of the first, second or third polynucleotide.

2. (Original) The isolated nucleic acid of claim 1, wherein the nucleic acid comprises a polynucleotide selected from the group consisting of the first polynucleotide, the second polynucleotide and a polynucleotide that is a complement of the first or second polynucleotide.

3. (Withdrawn) The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide that is identical to SEQ ID NO:2 at at least 1991 amino acid positions other than positions 558, 559, 618, 1027 and 1077.

4. (Withdrawn) The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide that is identical to SEQ ID NO:2 at at least 2001 amino acid positions other than positions 558, 559, 618, 1027 and 1077.

5. (Withdrawn) The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide that is identical to SEQ ID NO:2 at at least 2006 amino acid positions other than positions 558, 559, 618, 1027 and 1077.

6. (Withdrawn) The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide that is identical to SEQ ID NO:2 at at least 2010 amino acid positions other than positions 558, 559, 618, 1027 and 1077.

7. (Original) The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide having a histidine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively.

8. (Withdrawn) The isolated nucleic acid of claim 7, wherein the first polynucleotide encodes SEQ ID NO:2.

9. (Withdrawn) The isolated nucleic acid of claim 8, wherein the first polynucleotide is nucleotides 1 to 6048 of SEQ ID NO:1.

10. (Original) The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide having an arginine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively.

11. (Withdrawn) The isolated nucleic acid of claim 10, wherein the first polynucleotide encodes SEQ ID NO:4.

12. (Withdrawn) The isolated nucleic acid of claim 11, wherein the first polynucleotide is nucleotides 1 to 6048 of SEQ ID NO:3.

13. (Original) The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide having a histidine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted.

14. (Withdrawn) The isolated nucleic acid of claim 13, wherein the first polynucleotide encodes SEQ ID NO:6.

15. (Withdrawn) The isolated nucleic acid of claim 14, wherein the first polynucleotide is nucleotides 1 to 6045 of SEQ ID NO:5.

16. (Original) The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide having an arginine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted.

17. (Currently amended) ~~The isolated nucleic acid of claim 16, wherein the first polynucleotide encodes~~ An isolated nucleic acid comprising a polynucleotide selected from the group consisting of:

- (1) a first polynucleotide that encodes SEQ ID NO:8,
- (2) a second polynucleotide that is at least 80% identical to the first polynucleotide over the entire length of the first polypeptide and encodes an arginine at amino acid position 1027,
- (3) a third polynucleotide that encodes SEQ ID NO:8 with a conservative substitution, deletion or rearrangement at one or more non-critical amino acid position and an arginine at amino acid position 1027, and
- (4) a fourth polynucleotide that is a complement of the first, second or third polynucleotide.

18. (Original) The isolated nucleic acid of claim 17, wherein the first polynucleotide is nucleotides 1 to 6045 of SEQ ID NO:7.

19. (Original) A genetic construct comprising the polynucleotide of claim 1 operably linked to a non-native expression control sequence.

20. (Currently amended) A cell comprising a polynucleotide selected from the group consisting of (1) a polynucleotide that encodes an SCN5A polypeptide having a histidine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, (2) a polynucleotide that encodes an SCN5A polypeptide having an arginine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, (3) a polynucleotide that encodes an SCN5A polypeptide having a histidine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, and (4) a polynucleotide that encodes an SCN5A polypeptide having an arginine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted,

wherein each polynucleotide is operably linked to a non-native expression control sequence.

21. (Withdrawn) The cell of claim 20, wherein the cell comprises a polynucleotide that encodes an SCN5A polypeptide having a histidine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, and wherein the polynucleotide is operably linked to a non-native expression control sequence.

22. (Withdrawn) The cell of claim 21, wherein the polynucleotide encodes SEQ ID NO:2.

23. (Original) The cell of claim 20, wherein the cell comprises a polynucleotide that encodes an SCN5A polypeptide having an arginine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, and wherein the polynucleotide is operably linked to a non-native expression control sequence.

24. (Withdrawn) The cell of claim 23, wherein the polynucleotide encodes SEQ ID NO:4.

25. (Original) The cell of claim 20, wherein the cell comprises a polynucleotide that encodes an SCN5A polypeptide having a histidine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, and wherein the polynucleotide is operably linked to a non-native expression control sequence.

26. (Withdrawn) The cell of claim 25, wherein the polynucleotide encodes SEQ ID NO:6.

27. (Original) The cell of claim 20, wherein the cell comprises a polynucleotide that encodes an SCN5A polypeptide having an arginine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, wherein the polynucleotide is operably linked to a non-native expression control sequence.

28. (Currently amended) The cell of claim 27, wherein the polynucleotide A cell comprising a polynucleotide that encodes SEQ ID NO:8, wherein the polynucleotide is operably linked to a non-native expression control sequence.

29. (Original) The cell of claim 20, wherein the cell is from a human embryonic kidney cell line.

30. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first or third polynucleotide of claim 1.

31. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide of claim 1.

32. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 3.

33. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 4.

34. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 5.

35. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 6.

36. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 7.

37. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 8.

38. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 10.

39. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 11.

40. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 13.

41. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 14.

42. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 16.

43. (Canceled) An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 17.

44. (Canceled) An antibody that binds specifically to a polypeptide of claim 31.

45. (Canceled) A method for identifying an agent that can alter the activity of a sodium channel, the method comprising the steps of:
providing a cultured cell according to claim 20;
exposing the cell to a test agent;
determining sodium channel activity of the cell; and
comparing the sodium channel activity to that of a control cell that is not exposed to the test agent wherein a difference in sodium channel activity indicates that the agent can alter the activity of the sodium channel.

46. (Canceled) The method of claim 45, wherein the determining step comprises measuring a parameter selected from the group consisting of a sodium current across a cellular membrane, a membrane potential, and an intracellular sodium level.

47. (Canceled) A method for identifying an agent that can alter the expression of a sodium channel, the method comprising the steps of:

- exposing a cell that contains a first polynucleotide in claim 1 to a test agent wherein the expression of the polynucleotide is under the control of its native control sequences;
- determining the expression level of the polynucleotide at the mRNA or protein level; and
- comparing the expression level to that of a control cell that is not exposed to the test agent wherein a difference in expression level indicates that the agent can alter the expression of the sodium channel.

48. (Canceled) A method for determining whether a biological sample or a preparation derived from the biological sample contains a polypeptide of claim 32 or a nucleic acid encoding the polypeptide, the method comprising the steps of:

- contacting the sample or preparation with a polynucleotide probe, a pair of polynucleotide primers or an antibody specific for the nucleic acid or polypeptide; and
- determining whether the probe or antibody specifically binds to a component in the sample or preparation, or the primers specifically amplify a component of the sample, said binding or amplification being an indication that the sample contains the nucleic acid or polypeptide.

49. (Canceled) A method for determining whether a mutation on a sodium channel is associated with a disease comprising the step of:

- introducing the mutation into the first polynucleotide of claim 1; and
- determining the effect of the mutation in a suitable model for the disease.

50. (Canceled) A method for determining whether a human or non-human subject is at risk for Long QT syndrome, the method comprising the step of:

determining whether the subject carries an M1766L mutation on an SCN5A variant selected from the group consisting of (1) a variant having a histidine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, (2) a variant having an arginine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, (3) a variant having a histidine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, and (4) a variant having an arginine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted,

wherein an M1766L mutation on a (1), (2) or (3) variant indicates that the subject is at risk for Long QT syndrome, and wherein an M1766L mutation on a (4) variant indicates that the subject is not at risk for Long QT syndrome.

51. (Previously presented) The cell of claim 28, wherein the polynucleotide is nucleotides 1 to 6045 of SEQ ID NO:7.